Low-dose buprenorphine initiation during pregnancy: a case report

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Buprenorphine is recommended for pregnant patients with opioid use disorder. Traditional buprenorphine initiation requires moderate withdrawal symptoms to prevent precipitating withdrawal. Low-dose buprenorphine initiation is newly emerging and does not require withdrawal prior to initiation.

Case 1 is a 30-year-old pregnant patient with opioid use disorder. Inpatient rapid buprenorphine initiation precipitated withdrawal. Low-dose buprenorphine initiation was started twice, 1 outpatient and 1 inpatient with nonprescribed opioid use between. Case 2 is a 28-year-old pregnant patient with opioid use disorder. The patient started an inpatient low-dose buprenorphine initiation and planned its completion at home after discharge. Neither patient experienced precipitated withdrawal during their low-dose initiations.

These buprenorphine initiations in pregnant patients guided by a low-dose initiations protocol using only split buprenorphine-naloxone films represent an alternative opioid use disorder treatment method with potentially high acceptability. Future work is warranted to advance the evidence base informing clinicians on how to optimally individualize buprenorphine initiations in pregnancy.

Key words: buprenorphine induction, buprenorphine, case report, opioid use disorder, pregnancy

Introduction

The proportion of opioid-related deaths in pregnant individuals has increased steadily in recent years, and drug overdoses are a major cause of mortality in this population.[1] In pregnancy, buprenorphine is comparable with methadone in safety and efficacy and is currently a recommended treatment for opioid use disorder in pregnant individuals.[2,3]

Buprenorphine is a partial agonist at mu-opioid receptors. Precipitated withdrawal can be induced in individuals using a full agonist.[4] To prevent this, traditional buprenorphine initiation requires patients to be in moderate withdrawal initially. This poses an obstacle because discomfort and withdrawal symptoms are associated with poor treatment adherence.[5,6]

Low-dose buprenorphine initiation is a newly emerging method, which does not require withdrawal prior to initiation. However, there continues to be a dearth of information in the literature about how to best perform these initiations, particularly in pregnancy. We present 2 cases of buprenorphine initiations in pregnant patients where treatment was guided by a low-dose initiations protocol using only split buprenorphine-naloxone films in both the inpatient and outpatient settings.

Case 1

The patient is a 30-year-old G3P0020 with a history of depression and anxiety. Her prenatal course was complicated by recurrent urinary tract infections and anemia treated with iron infusions. Substance use history includes opioids, stimulants, cannabis, and nicotine. The patient had no previous buprenorphine initiation in pregnancy.

The patient self-presented to the antepartum service for inpatient admission to initiate buprenorphine at 15 5/7 weeks of gestation. the patient reported regular fentanyl use, and her Clinical Opioid Withdrawal Scale (COWS) was 2 on admission. After informed consent, a rapid low-dose buprenorphine induction was started (Table 1). The schedule was to administer 0.5 mg up to every 3 hours on day 1, then 1 mg every 3 hours on day 2, and 12 mg on day 3 with 2 mg as needed. The second dose of 0.5 mg precipitated withdrawal with a COWS score of 24. The dose was reduced to 0.5 mg twice per day starting on day 2, but the patient declined buprenorphine and left against medical advice.

The patient remained in contact with our clinic and started a home initiation at 18 0/7 weeks of gestation. The schedule was modified to decrease the risk of precipitating withdrawal, and the patient was provided with instructions on how to do a home low-dose initiation similar to that described in Table 2.[7] The patient was instructed on how to cut the films to the correct dose. Harm reduction principles in the setting of continued nonprescribed opioid use while undergoing the induction were discussed. At a virtual visit on day 5 of

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Both patients gave informed consent. The signed consent forms will be available upon request.

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TABLE 1
Rapid buprenorphine initiation for patient case 1 during her first inpatient admission

Day	Buprenorphine dose	Time administered	Buprenorphine-naloxone film division	Max COWS score
1	0.5 mg	15:00	1/4 of 2/0.5 mg	24
	0.5 mg	17:36	1/4 of 2/0.5 mg	
2	Left hospital AMA			

AMA, against medical advice; *COWS*, Clinical Opioid Withdrawal Scale.

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the initiation, the patient reported taking 4 mg twice a day and experiencing mild rhinorrhea and agitation; the patient was instructed to continue the initiation schedule as planned. At the patient's next appointment at 20 0/7 weeks of gestation, the patient disclosed that she had stopped buprenorphine and had been using fentanyl the week earlier. The patient opted to receive instructions on how to restart the low-dose home buprenorphine initiation at home.

The patient was admitted and treated for pyelonephritis at 21 6/7 weeks of gestation and requested restarting buprenorphine during the admission. The plan was made for her to remain inpatient until the dose was uptitrated to 4 mg twice a day using the low-dose buprenorphine protocol in Table 2 while the patient underwent treatment for pyelonephritis (and its associated pain). For moderate withdrawal symptoms (COWS score > 8), an additional 0.5 mg buprenorphine was made available with each dose spaced at least 3 hours apart[7]; however, the patient did not require any doses (Table 3). The patient was discharged on day 6 with instructions to uptitrate to buprenorphine-naloxone 8/2 mg twice a day and continue at this dose until her follow-up appointment with our clinic.

TABLE 2
Low-dose buprenorphine initiation schedule[a]

Day	Buprenorphine dose	Buprenorphine-naloxone film division
1	0.5 mg	1/4 of 2/0.5 mg
2	0.5 mg	1/4 of 2/0.5 mg
	0.5 mg	1/4 of 2/0.5 mg
3	1.0 mg	1/2 of 2/0.5 mg
	1.0 mg	1/2 of 2/0.5 mg
4	2.0 mg	One 2/0.5 mg
	2.0 mg	One 2/0.5 mg
5	4.0 mg	1/2 of 8/2.0 mg
	4.0 mg	1/2 of 8/2.0 mg
6	8.0 mg	One 8/2.0 mg
	8.0 mg	One 8/2.0 mg

On days 1 to 5, if moderate withdrawal symptoms (COWS score ≥ 8), 0.5 mg as needed every 3 hours can be added. Day 7 and onward, continue to increase dose as clinically indicated (eg, persistent withdrawal symptoms or cravings).

COWS, Clinical Opioid Withdrawal Scale.

[a] As stated in the manuscript, this protocol is meant to be an example of how to initiate buprenorphine for patients presenting without moderate withdrawal and/or with continued use of full agonist opioids. It is important to individualize buprenorphine dosing to patient presentation over time (eg, may be warranted to provide higher buprenorphine doses than described here, such as 8 to 24 mg with emergence of moderate withdrawal symptoms, COWS score > 8).[7]

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Case 2

The patient is a 28-year-old G6P4014 with a history of bipolar disorder and anxiety. Her prenatal course was uncomplicated. Substance use history includes opioids, stimulants, cannabis, and nicotine. The patient had no previous buprenorphine initiation in pregnancy.

The patient presented to the antepartum service for inpatient admission to initiate buprenorphine at 17 0/7 weeks of gestation. The patient reported the use of heroin and fentanyl, and the COWS score was 1 on admission. After consent, the patient was started on low-dose buprenorphine initiation protocol described for patient 1 (Table 2).[7] With this protocol, 0.5 mg buprenorphine doses every 3 hours were available as needed for a COWS score of ≥8; the patient received additional 0.5 mg doses on days 1 and 2 for moderate withdrawal symptoms (Table 4). The patient requested discharge on day 3; the patient was provided with instructions to uptitrate to 2 mg twice a day on day 4, 4 mg twice a day on day 5, and 8 mg twice a day on day 6, continuing at this dose until her next appointment. The patient missed her clinic follow-up. On the phone with clinic nurses, the patient reported using nonprescribed opioids every 2 to 3 days. The nurses provided instructions on how to restart the same low-dose buprenorphine initiation at home with harm reduction strategies in the setting of ongoing nonprescribed opioid use.

Discussion

A major benefit of low-dose buprenorphine initiation is that withdrawal symptoms are not necessary to begin the initiation. The limitations of this approach include hospital admission time (if inpatient), availability of formulations and doses (films or transdermal formulations), and provider comfort.

Multiple low-dose buprenorphine protocol options have been shared. For example, in a rapid microdosing initiation protocol, buprenorphine is administered before withdrawal symptoms present, and doses are given every 3 to

TABLE 3
Low-dose buprenorphine initiation for patient case 1 during her second inpatient induction

Day	Buprenorphine dose	Time administered	Buprenorphine-naloxone film division	Max COWS score
1	0.5 mg	16:21	1/4 of 2/0.5 mg	4
2	0.5 mg	09:43	1/4 of 2/0.5 mg	7
	0.5 mg	21:06	1/4 of 2/0.5 mg	
3	1.0 mg	09:12	1/2 of 2/0.5 mg	1
	1.0 mg	21:32	1/2 of 2/0.5 mg	
4	2.0 mg	09:03	One 2/0.5 mg	3
	2.0 mg	21:13	One 2/0.5 mg	
5	4.0 mg	10:31	One 4/1 mg	1
	4.0 mg	21:21	One 4/1 mg	
6	8.0 mg	09:05	One 8/2 mg	1
	Discharged with instructions to continue buprenorphine-naloxone 8/2 mg twice a day			

COWS, Clinical Opioid Withdrawal Scale.

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4 hours.[4] This method is time-effective; however, patients are generally inpatient, and there may be a risk of precipitating withdrawal, as seen in our patient in case 1. Another protocol is the Bernese method where repetitive very low doses of buprenorphine are administered at extended intervals overlapping with full agonist use.[8] A limitation of this method can be provider reluctance to prescribe full agonists, despite the safety of their use concurrent with buprenorphine when administered in an individualized fashion.

Galati et al[9] described an alternative initiation protocol in pregnant patients where a transdermal patch was administered as a bridge to sublingual buprenorphine, sparing patients from withdrawal symptoms. However, economic barriers can limit the availability of buprenorphine patches. Coish and Hardial[10] reported a case of a pregnant patient who completed a 17-day low-dose outpatient buprenorphine initiation. A drawback is its prolonged course the prolonged course.

TABLE 4
Low-dose buprenorphine induction for patient case 2 during her inpatient admission

Day	Buprenorphine dose	Time administered	Buprenorphine-naloxone film division	Max COWS score
1	0.5 mg	13:52	1/4 of 2/0.5 mg	9
	0.5 mg	21:17	1/4 of 2/0.5 mg	
2	0.5 mg	09:58	1/4 of 2/0.5 mg	12
	0.5 mg	17:00	1/4 of 2/0.5 mg	
	0.5 mg	21:15	1/4 of 2/0.5 mg	
3	1.0 mg	09:26	1/2 of 2/0.5 mg	7
	1.0 mg	20:27	1/2 of 2/0.5 mg	
Patient discharged with instructions to complete low-dose induction at home.				

COWS, Clinical Opioid Withdrawal Scale.

Reddy. Low-dose buprenorphine induction in pregnancy. Am J Obstet Gynecol Glob Rep 2024.

Although precipitated withdrawal successfully did not occur with the low-dose initiation in these cases, the patient in case 2 developed withdrawal symptoms during her inpatient initiation. The patient received additional 0.5 mg doses on the first 2 days, to improve her symptoms. However, the patient's request for discharge brought up the concern that her withdrawal symptoms on hospital day 3 may have been undertreated. Herring et al[11] described giving 4 to 8 mg of buprenorphine initially to manage opioid withdrawal. Thus, in this protocol, the additional 0.5 mg every 3 hours as needed is intended to be a starting point. The dose and schedule should be modified based on patient factors. Importantly, in the setting of a history of fentanyl use and a patient presentation of moderate withdrawal (COWS score > 8), the administration of much higher buprenorphine doses is commonly recommended (8−24 mg).[7]

Inpatient buprenorphine initiation may be recommended because of the availability of medications to manage symptoms in a controlled environment. However, social factors, including childcare and increased family support in a familiar environment, can make patients motivated to complete outpatient buprenorphine initiations. It is important that future work elucidating clinical guidance for low-dose buprenorphine initiations be adaptable for both the inpatient and outpatient settings, to optimize patient-centeredness.

In this article, we proposed a low-dose buprenorphine initiation protocol (Table 2) that was used to guide the treatment of 2 patients.[7] This protocol only used split buprenorphine-naloxone films and took less than a week. Although this exact protocol was used in these cases, we emphasize that buprenorphine dosing should be individualized to the patient's clinical presentation, which may include higher buprenorphine doses (eg, 16 mg with sufficient withdrawal), more frequent dosing, and use of full opioid agonists concurrent with buprenorphine as clinically indicated. As seen in our

patients, emerging clinical protocols should be developed for both the inpatient and outpatient settings, allowing patient flexibility. More studies are warranted to test the safety and efficacy of low-dose buprenorphine protocols in pregnancy and after delivery, given their promise to expand treatment initiation rates and improve medication adherence in the ongoing overdose and maternal mortality crises. ■

CRediT authorship contribution statement

Shivania Reddy: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Caitlin E. Martin:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing.

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